



The Dow Chemical Company
Midland, Michigan 48674

December 4, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1060
Rockville, MD 20852

**Re: Docket No. 00D-1539, Draft Guidance for Industry: Electronic Records;
Electronic Signatures, Maintenance of Electronic Records**

Dear Sir or Madam:

The Dow Chemical Company ("Dow") welcomes the opportunity to comment on FDA's draft guidance under 21 CFR Part 11 concerning maintenance of electronic records.¹ Dow manufactures active pharmaceutical ingredients ("APIs") and excipients. Dow's comments relate to the applicability of the proposed guidance and to the technical feasibility of the draft guidance.

1. **The Applicability Section of the Draft Guidance Would Improperly Extend Part 11's Coverage to Electronic Records Maintained in Connection With the Manufacture of APIs and Excipients, Which Are Not Required by Agency Regulations.**

By its terms, the draft guidance would apply to electronic records maintained by manufacturers of APIs and excipients. Part 11 does not apply to such records, because they are not required by any agency regulations. They are required by the Federal Food, Drug, and Cosmetic Act (the "Act"), as indicated by FDA guidance, but neither the Act nor the guidance is an agency regulation within the meaning of Part 11.

Section 2.1 of the draft guidance purports to define the applicability of Part 11:

Part 11 applies to electronic records and electronic signatures that persons create, modify, maintain, archive, retrieve, or transmit under any records or signature requirement set forth in the Federal Food, Drug, and Cosmetic Act (the Act), the Public Health Service Act (PHS Act), or any FDA regulation. Any requirements set forth in the Act, the PHS Act, or any FDA regulation, with the exception of part 11, are referred to in this document as predicate rules. Most predicate rules are contained in Title 21 of the Code of Federal Regulations. In general, predicate rules address the research, production, and control of FDA regulated articles, and fall into several broad categories. Examples of such categories include, but are not limited to: manufacturing

¹ The draft guidance is available at <http://www.fda.gov/ohrms/dockets/dockets/00d1539/00d1539.htm> (entry for 9/4/02). Notice of availability of the draft guidance was announced at 67 Fed. Reg. 56848 (Sept. 5, 2002).

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practices, laboratory practices, clinical and pre-clinical research, adverse event reporting, product tracking, and pre and post marketing submissions and reports. However, this draft guidance only applies to records that, by predicate rule, you are required to maintain. [Emphasis added.]

This is a restatement of the text of Part 11's scope section, particularly 21 CFR § 11.1(b):

This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements **set forth in agency regulations**. This part also applies to electronic records **submitted to** the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means. [Emphasis added.]

The emphasized language limits the scope of Part 11 to those electronic records required by FDA regulations to be maintained, and to electronic records submitted to FDA under the Act or the PHS Act. FDA has defined the term "regulations" to mean:

an agency rule of general or particular applicability and future effect issued under a law administered by the Commissioner or relating to administrative procedures. In accordance with § 10.90(a), each agency regulation will be published in the Federal Register and codified in the Code of Federal Regulations.²

In contrast, the draft guidance does not limit the scope of Part 11 in that manner. Instead, it identifies the Act and the PHS Act as sources of recordkeeping requirements subject to Part 11 independent of FDA regulations. As seen from Part 11 itself, the Act and the PHS Act trigger Part 11 only with respect to electronic records submitted to FDA; they do not trigger Part 11 with respect to electronic records maintained by companies and not submitted to FDA. The statement in the draft guidance that "[m]ost predicate rules are contained in Title 21 of the Code of Federal Regulations" violates the requirement in the definition of "regulations" that all regulations be published in the Code of Federal Regulations.

This distinction relates directly to records maintained by manufacturers of APIs and excipients. FDA has no regulations governing current good manufacturing practices ("cGMPs") applicable to the manufacture of APIs and excipients. Part 211 governs only "current good manufacturing practice for preparation of drug products"³, i.e., finished dosage form pharmaceuticals.⁴ Thus, there are no "agency regulations" to trigger Part 11 for records maintained under cGMPs for the manufacture of APIs and excipients.⁵

² 21 CFR § 10.3(a) (definition of "regulations").

³ 21 CFR § 211.1(a).

⁴ 21 CFR § 210.3(b)(4).

⁵ See 43 Fed. Reg. 45014, 45026 (Sept. 29, 1978) ("Although these CGMP regulations [Part 211] are not applied to the manufacture of bulk drug components, there are numerous instances where good manufacturing practices for bulk drug components would parallel the requirements set forth in Part 211.

The Act itself does establish a general requirement to use cGMPs in manufacturing APIs and excipients.⁶ FDA has issued detailed guidance on the meaning of this statutory requirement with respect to the manufacture of APIs.⁷ The guidance addresses electronic recordkeeping.⁸ Nevertheless, that guidance is not an agency regulation.⁹

Accordingly, it is inappropriate for FDA to state in the draft guidance that the Act and the PHS Act count as predicate rules triggering Part 11. They can trigger Part 11 only with respect to electronic records submitted to FDA. They cannot trigger Part 11 with respect to electronic records maintained by API and excipient manufacturers pursuant to the Act's requirement for cGMPs. The present language in the draft guidance impermissibly extends the scope of Part 11 beyond the limits established in Part 11 itself.

The applicability language of this draft guidance is virtually identical to that in other draft guidance documents on Part 11.¹⁰ Thus, these comments should also be applied to those draft documents as well.

2. Maintenance of Electronic Records Without Alteration or Loss of Data Is Technically Infeasible.

The draft guidance articulates many FDA expectations about the performance expected to meet Part 11's requirement to protect electronic records "to enable their accurate and ready retrieval throughout the records retention period."¹¹ FDA should recognize, however, that these expectations might not be feasible to meet in many instances. Accordingly, FDA should revise the draft guidance to recognize the technical feasibility problems inherent in meeting the requirement.

For this reason, FDA will utilize the standards of Part 211 as guidelines during inspections of manufacturers of bulk drug components under the jurisdiction of the act.”)

⁶ Section 501(a)(2)(B) of the Act, 21 USC § 351(a)(2)(B), declares a drug to be adulterated if “the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.” (Emphasis added.) A “drug” includes “articles intended for use as a component of” a finished form pharmaceutical. Section 201(g), 21 USC § 321(g)(1).

⁷ FDA, “Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients” (Aug. 2001) (“Q7A”), available at www.fda.gov/cder/guidance/4286fml.pdf. A Federal Register notice announcing availability of the guidance is at 66 Fed. Reg. 49028 (Sept. 25, 2001).

⁸ See particularly Q7A § 5.4, “Computerized Systems”. Nowhere in Q7A does FDA indicate that Part 11 applies to electronic records maintained by API manufacturers.

⁹ Q7A begins, as do many FDA guidance documents, with the statement, “This guidance represents the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.” See also 21 CFR § 10.115, “Good Guidance Practices”.

¹⁰ See Section 2.1 of the draft guidance documents on Glossary of Terms (Aug. 2001), Validation (Aug. 2001), Time Stamps (Feb. 2002), and Electronic Copies of Electronic Records (August 2002).

¹¹ 21 CFR § 11.10(c).

a. **The Technical Problems Are Unsolved.**

In many cases it may not be technically feasible to meet the Part 11 maintenance requirement. In others the cost may be economically infeasible. Some of the reasons are explained in a *Scientific American* article¹² cited by the Justice Department in a guide to federal agencies on implementing electronic processes.¹³

The article first explains in laymen's terms that digital documents are essentially programs in need of software to read them:

Digital information can be saved on any medium that is able to represent the binary digits ("bits") 0 and 1. We will call an intended, meaningful sequence of bits, with no intervening spaces, punctuation, or formatting, a bit stream

[I]nterpreting a bit stream depends on understanding its implicit structure, which cannot be explicitly represented in the stream. A bit stream that represents a sequence of alphabetical characters may consist of fixed-length chunks ("bytes"), each representing a code for a single character To extract the bytes from the bit stream, thereby "parsing" the stream into its components, we must know the length of a byte

Most files contain information that is meaningful solely to the software that created them For convenience, we call such embedded information—and all other aspects of a bit stream's representation, including byte length, character code and structure—the encoding of a document file. These files are essentially programs: instructions and data that can be interpreted only by appropriate software. A file is not a document in its own right—it merely describes a document that comes into existence when the file is interpreted by the program that produced it. Without this program (or equivalent software), the document is a cryptic hostage of its own encoding

As FDA identified in the draft guidance, the only options are maintaining legacy systems or migrating the data. The article identifies "serious shortcomings" with the idea of maintaining legacy systems, related to both software and hardware:

[To read old digital documents,] we must save the programs that generate our digital documents, as well as all the system software required to run those programs. Although this task is monumental, it is theoretically feasible.

Preserving software is not sufficient, however; hardware must also be preserved:

¹² Jeff Rothenberg, "Ensuring the Longevity of Digital Documents", *Scientific American*, Vol. 272, No. 1 (Jan. 1995), pp. 42-47.

¹³ See U.S. Department of Justice, "Legal Considerations in Designing and Implementing Electronic Processes: A Guide for Federal Agencies" (Nov. 2000), n. 10, available at www.cybercrime.gov/eprocess.pdf.

How can we provide the hardware to run antiquated systems and application software? A number of specialized museums and “retro-computing” clubs are attempting to maintain computers in working condition after they become obsolete. Despite a certain undeniable charm born of its technological bravado, this method is ultimately futile. The cost of repairing or replacing worn out components (and retaining the expertise to do so) must inevitably outweigh the demand for any outmoded computer.

Next, the article addresses the problems with migrating, or “translating”, data as software changes:

Is it necessary to run the specific program that created a document? In some cases, similar software may at least partially be able to interpret the file. Still, it is naive to think that the encoding of any document—however natural it may seem to us—will remain readable by future software for very long. Information technology continually creates new schemes, which often abandon their predecessors instead of subsuming them

Translating a document into successive short-term standards offers false hope. Successive translation avoids the need for ultimate standards [which are not available now], but each translation introduces new losses

Finally, translation suffers from a fatal flaw. Unlike English and ancient Greek, whose expressive power and semantics are roughly equivalent, digital documents are evolving so rapidly that shifts in the forms of documents must inevitably arise. New forms do not necessarily subsume their predecessors or provide compatibility with previous formats. Old documents cannot always be translated into unprecedented forms in meaningful ways, and translating a current file back into a previous form is often impossible. For example, many older, hierarchical databases were completely redesigned to fit the relational model, just as relational databases are now being restructured to fit emerging object-oriented models. Shifts of this kind make it difficult or meaningless to translate old documents into new standard forms.

If digital documents and their programs are to be saved, their migration must not modify their bit streams, because programs and their files can be corrupted by the slightest change . . . Although bit streams can be designed to be immune from any expected change, future migration may introduce unexpected alterations. For example, aggressive data compression may convert a bit stream into an approximation of itself, precluding a precise reconstruction of the original. Similarly, encryption makes it impossible to recover an original bit stream without the decryption key.

The bottom line is that Part 11’s archiving requirement, maintaining digital documents without alteration, may be currently technologically infeasible.

b. The Federal Government Has Been Unable to Find a Solution.

The federal government itself has been wrestling with the problem of how to archive electronic records without data loss, and has been unable to come up with a solution. FDA cannot reasonably expect the regulated entities subject to Part 11 to comply with the record maintenance requirement when the federal government has been unable to do so after spending millions of dollars trying.

A recent report for the National Archives and Records Administration (“NARA”) describes the current state of affairs:

Government employees do not know how to solve the problem of electronic records – whether the electronic information they create constitutes records and, if so, what to do with the records. Electronic files that qualify as records—particularly in the form of e-mail, and also word processing and spreadsheet documents—are not being kept at all as records in many cases and are frequently not being scheduled. Employees lack guidance and knowledge concerning how to identify electronic records and what to do with them once identified. Technology tools for managing electronic records do not exist in most agencies. The agency information technology environments have not been designed to facilitate the retention and retrieval of electronic records. Despite the growth of electronic media, agency records systems are predominately in paper format rather than electronic. Virtually every agency visited indicated that the official policy is that their records will be maintained in paper format. Yet the agencies recognize that most records are now created in an electronic environment—in word-processing documents, spreadsheets, databases, and the like. The predominate e-mail policy is to print out e-mails that are considered records and to save the paper copies. The chief paradox of today’s Federal RM [records management] is the disconnect between paper and electronic recordkeeping.¹⁴

NARA itself has recognized the technological challenges:

Because long-term temporary and permanent electronically signed records have greater longevity than typical software obsolescence cycles, it is virtually certain that agencies will have to migrate those records to newer versions of software to maintain access. The software migration (as opposed to media migration) process may invalidate the digital signature embedded in the record. This may adversely affect an agency’s ability to recognize or enforce the legal rights documented in those records.¹⁵

The Government Accounting Office has referred to this problem:

¹⁴ SRA International, Inc., “Report on Current Recordkeeping Practices within the Federal Government, Prepared for the National Archives and Records Administration” (Dec. 10, 2001), available at www.nara.gov/records/rmi.html at 5-6 (emphasis in original).

¹⁵ NARA, “Records Management Guidance for Agencies Implementing Electronic Signature Technologies” (Oct. 18, 2000), available at www.nara.gov/records/policy/gpea.html, § 5.5 (emphasis in original).

The long-term preservation and retention of those electronic records is also a challenge since providing continued access to archived records over many generations of systems is difficult. The average life of a typical software product is 2 to 5 years.¹⁶

So has the Justice Department:

Agencies should consider several factors related to the accessibility of electronic records. First, computer technology is rapidly changing and software and formatting standards may quickly become obsolete. Computer-stored data may become useless unless the agency can provide the continued capability with the older technologies or can accurately translate the document as more modern systems are implemented. Second, if in the future, an agency no longer has staff who are familiar and competent to work with the electronic processes necessary to read older data, such data could be functionally unavailable. Electronic files might be stored while encrypted by software or protected by passwords no longer available or remembered years later, unless steps are taken to preserve the software or passwords.¹⁷

In summary, the federal government itself is not archiving electronic records electronically, nor has it solved the problem of how to do so for extended periods without data loss. What the federal government has been unable to achieve is unlikely to be feasible for the regulated community.

c. Examples of Infeasibility in the Draft Guidance

In § 6, the draft guidance describes two approaches to maintenance of electronic records, the time capsule approach and the electronic records migration approach. The draft guidance admits that the time capsule approach “may be of limited practicality for long-term maintenance of electronic records”, for reasons similar to those stated above. Yet in describing the migration approach, the draft guidance warns that “you should carefully consider when it would be prudent to discard the old electronic records and/or system”, because there could be a need to go back to the old system. In other words, to assure reliability, the draft guidance essentially endorses using both systems. That surely is infeasible for any extended period.

In § 6.2.1.5, the draft guidance recommends:

¹⁶ Government Accounting Office, “National Archives: Preserving Electronic Records in an Era of Rapidly Changing Technology”, GAO/GGD-99-94 (July 1999), available at www.gao.gov/archive/1999/gg99094.pdf.

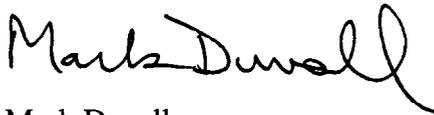
¹⁷ Department of Justice, “Legal Considerations in Designing and Implementing Electronic Processes: A Guide for Federal Agencies” (Nov. 2000), available at www.cybercrime.gov/eprocess.htm, § II.A.3 (footnote omitted).

Just prior to performing the electronic record migration a trusted third party from outside the organization that has some responsibility for the electronic record verifies the digital signature using the old system methods[.]

It is unclear whether the third party must come from outside the company maintaining the record, or only from outside the internal group maintaining the record. In either case, using a "trusted third party" is an awkward approach that would add greatly to complexity while providing little assurance of security.

In these and other provisions of the draft guidance, FDA should explicitly recognize the inherent difficulties in maintaining electronic records over time and indicate a tolerance for less than perfect results.

Sincerely,

A handwritten signature in black ink that reads "Mark Duvall". The signature is written in a cursive style with a large, sweeping "M" and a long, trailing flourish at the end.

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